NAVAL HEALTH RESEARCH CENTER

THE MANY FACES OF MENINGOCOCCAL DISEASE: A CASE SERIES AND REVIEW OF PRESENTATIONS AND TREATMENT OPTIONS

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The Many Faces of Meningococcal Disease:

A Case Series and Review of Presentations and Treatment Options

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Abstract

We present three cases of *Neisseria meningitidis* with varied clinical presentations, including meningococcemia, meningitis, and pneumonia. Our cases suggest an association between concomitant bacterial and viral infections, including group A *streptococcus* and adenovirus, and an increased risk of invasive *Neisseria* infections. Polymerase chain reaction data are a useful adjunct to bacterial cultures for the diagnosis. Our case series exemplify the continued high mortality of *N. meningitides* and highlights the need for more immunogenic vaccines for prevention.

Introduction

Neisseria meningitidis is a significant cause of morbidity and mortality worldwide and the leading cause of bacterial meningitis in the United States. Meningitis is the most common (80 to 85% of cases) presentation of *N. meningitidis*, but this Gram-negative diplococcus may also cause bacteremia, meningococcemia, or pneumonia. Uncommon presentations include pericarditis, arthritis, and conjunctivitis (1,2). Most cases in the United States are sporadic, although outbreaks are well described (3-5). Infection is transmitted person-to-person via aerosol secretions; up to 10% of healthy adults have nasopharyngeal colonization. Invasive disease occurs when the organism penetrates the mucosa and gains entrance into the bloodstream, leading to systemic meningococcal disease. Risk factors for the development of clinical disease include ages of 18 to 23 years, crowded living conditions such as college dormitories or military barracks (6), tobacco use (7), concomitant respiratory infection (8,9), and terminal complement deficiency (10). We describe three cases of *N. meningitidis* among military members evaluated at our institution over a 1-year period. Our cases exemplify both the potential variable clinical presentation and high risk of mortality.

Case 1

An 18-year-old white/Hispanic Marine Corps recruit awoke at 3:30 a.m. with a bilateral lower extremity rash that was palpable and extremely painful. He had no previous medical diagnoses and was taking no medications. One month prior, he had arrived from northern California to the training center, at which time he received a single dose of 1.2 million units of benzathine penicillin for prophylaxis against group A *streptococcus*, as well as pneumococcal (polyvalent pneumovax 23, Merck & Company, Inc.) and meningococcal (Menomune

quadrivalent polysaccharide vaccine, Aventis Pasteur, Inc.) vaccinations. He noted a 3-day history of cough and sore throat, but no headache or fevers. He reported to the medical clinic at 9:00 a.m., 6 hours after the rash began. He was in acute respiratory distress and reported intense myalgias. During the time of presentation, there was an ongoing outbreak of group A streptococcal pneumonia at the same training site (11).

Vital signs showed a temperature of 98.1º F, blood pressure of 79/41 mmHg, pulse of 140 beats/minute, and respiratory rate of 36. Oxygen saturation was 84% on a 12-L oxygen non-rebreather facemask. His skin examination showed a diffuse, palpable purpuric rash consistent with purpura fulminans (Figure 1). Conjunctival petechiae were also noted (Figure 2). Lung examination revealed tachypnea, accessory muscle use, and diffuse respiratory crackles. His heart sounds were normal except for tachycardia; there were no murmurs, rubs, or gallops. Neurological examination was initially unremarkable with normal mental status, no nuchal rigidity, and normal strength throughout.

The differential diagnosis included meningococcemia, toxic shock syndrome, and sepsis. Two liters of normal saline, as well as 2 g of ceftriaxone and 900 mg of clindamycin, were administered. His blood pressure increased to 122/68 mmHg, and he was transferred to our emergency room. On arrival, his systolic blood pressure was 90 mmHg, pulse 118, respiratory rate 36, and oxygen saturation 84% on 15 L of oxygen by facemask; he was intubated. Laboratories on admission included a blood gas with a pH of 6.84, pCO_2 103, and a pO_2 of 78; the white blood cell count was 20,200 cells/ml with 85% neutrophils, hemoglobin 14.5 g/dl, and platelet count 35,000. Chemistry panel and liver function testing revealed bicarbonate of 18 mEq/L, anion gap of 15, and albumin of 2.1 g/dl; transaminases were normal. A chest radiograph showed patchy to confluent airspace opacities throughout all the visualized lobes;

small biapical pneumothoraces and bilateral chest tubes were present. Cultures were unremarkable. During transfer to the intensive care unit, he became asystolic; the patient died, despite aggressive resuscitation efforts. On autopsy, he had multiple petechiae and small hemorrhages of his intestines, mesentery, renal cortex, adrenals, lungs, skeletal muscle, conjunctiva, myocardium, and epicardium (Figure 3). Skin was noteworthy for a purpuric rash of his face, trunk, and extremities. There was pulmonary edema, evidence of shock to multiple organs, and numerous microthrombi in the heart, lungs, liver, kidney, and brain. There was no purulent meningeal exudate. Polymerase chain reaction on the cerebrospinal fluid (CSF) (Centers for Disease Control and Prevention [CDC], Atlanta, Georgia, USA) was positive for *N. meningitidis* serogroup C. The cause of death was determined as *N. meningitidis* septicemia (meningococcemia).

Case 2

A 22-year-old active-duty female developed fevers, headaches, confusion, and a rash on her bilateral lower extremities. She had no significant past medical history and was taking only progesterone injections for contraception. She received routine vaccinations, including meningococcal immunizations (Menomune quadrivalent polysaccharide vaccine) in 1999 and January 2003. Her symptoms developed over 3 days while on vacation to visit her family, and she reported no ill contacts. On examination, she was mildly confused and had a temperature of 103º F with a normal blood pressure. Neurologic evaluation demonstrated nuchal rigidity without cranial nerve deficits. Skin examination revealed a palpable erythematous, petechial rash on her bilateral extremities extending to the thighs. Heart and lung examinations were unremarkable.

Laboratory values were significant for a white blood cell count of 13,200 cells/ml, with 79% neutrophils and 19% band forms; other peripheral values were normal. CSF was cloudy with a white blood count of 2,320, 96% neutrophils, protein 581 mg/dl, and glucose 23 mg/dl. The patient was initially treated with ceftriaxone, vancomycin, and dexamethasone. Dilantin was also administered for seizure prophylaxis. Latex agglutination for *N. meningitidis* in the CSF was positive, but the culture and Gram stain were negative. One of two blood cultures grew *N. meningitidis* serogroup B sensitive to ceftriaxone and penicillin. The patient defervesced, and her mental status cleared over a 3-day period. She completed a 14-day course of ceftriaxone. A CH50 level was normal, and she had no personal or family history of *Neisseria* infection. The patient had complete resolution of all symptoms without neurologic deficits.

Case 3

A 32-year-old white/Hispanic male in his 20th day of military recruit training presented with a fever of 103º F and enuresis. Three weeks earlier, he had arrived from Texas; at that time, he received an injection of benzathine penicillin for group A *streptococcus* prophylaxis, as well as meningococcal and pneumococcal vaccinations. He had no known medical problems and was HIV negative. His enuresis was judged secondary to not getting out of bed at night to void; a urinalysis was unremarkable. The patient had a concurrent cough, fevers, and upper respiratory symptoms for which a chest radiograph was ordered but not obtained by the patient. On a follow-up visit 4 days later, his cough was improved, and his vital signs were within normal limits.

Two days later, he collapsed during a training exercise from acute respiratory distress and developed pulseless ventricular fibrillation. His temperature was 105^{o}F. Attempts at resuscitation were unsuccessful. No laboratory tests were obtained prior to death. At autopsy, a

multilobar acute pneumonia was noted without other significant findings; there was no evidence of cardiac or central nervous system (CNS) disease. Multiple samples of lung tissue were positive for *N. meningitidis* by culture, PCR evaluation (sequence confirmed), and immunohistochemistry analysis; the organism was not groupable (Naval Health Research Center, San Diego, California; Walter Reed Army Institute of Research, Silver Spring, Maryland; and the CDC). Blood and CSF were negative for evidence of *N. meningitidis* by culture and PCR, but brain tissue was weakly PCR positive. Lung tissue and blood were also positive for adenovirus type 4 by PCR, using universal and adenovirus serotype 4-specific primers. The case occurred during an adenoviral outbreak at the recruit camp. Lung tissue was also culture and PCR positive for *Haemophilus influenzae*. The cause of death was determined to be cardiopulmonary arrest secondary to multilobar pneumonia caused by *N. meningitidis* with concomitant adenovirus and *H. influenza* infections.

Discussion

N. meningitidis has a variety of clinical presentations, including meningococcemia with purpura fulminans, meningitis, and pneumonia. All of our cases occurred in young military members, and two cases occurred during outbreaks of respiratory infections (group A *streptococcus* and adenovirus type 4), suggesting that concomitant viral and bacterial infections increase the risk of invasive disease. Our two fatal cases demonstrate the significant mortality of meningococcal disease despite medical advances. All patients had previously received the meningococcal quadrivalent polysaccharide vaccine.

Vieusseux first described meningococcal disease in 1805, and the causative organism was identified in 1887 (12-14). Worldwide, *N. meningitidis* accounts for 500,000 infections and 50,000 deaths annually (15). Within the United States, the annual incidence is 0.9 to 1.5 cases

per 100,000, and 98% of cases are sporadic (12). Disease incidence is highest among infants after maternal antibodies wane and in young adults ages 15 to 23 years. Although the disease is most common in young children, case-fatality rates are highest in the teenage years. Infection occurs when virulent *N. meningitidis* organisms are acquired during close contact with a colonized host; the bacterium must hematogenously disseminate, while the host lacks immunity to that specific serogroup.

Risk factors for disease development include concurrent respiratory infection, which may decrease the integrity of the mucosal barrier (7,8). Respiratory illness may also increase the risk of *N. meningitidis* transmission due to increased cough and secretions (12). Crowded living conditions, such as college dormitories and military barracks, have been associated with a heightened disease incidence (12, 16). Among military members, military recruits have the highest risk due to crowding and arrival from diverse locations throughout the United States (6). Other risk factors include tobacco smoke and indoor fire exposure, which likely interfere with mucosal integrity; all of our cases were in non-smoke environments.

Immunodeficiencies, including terminal complement deficiency, properdin deficiency, asplenia, and HIV infection predispose to meningococcal disease (9, 17). Of patients with a single meningococcal infection, 5 to 10% are found to be complement C5-C9 deficient, whereas those with multiple episodes have a 30% prevalence of deficiency (18). All patients in this case series were HIV seronegative and had normal splenic function; only one could be tested (case 2) for complement deficiency and had a normal level. None of the cases had family or personal histories remarkable for *Neisseria* infections or meningitis.

Other potential host factors that may play a role in susceptibility and severity of the infection include alterations of plasminogen activator inhibitor type 1, Toll-like receptor 4,

Fcgamma-receptors, tumor necrosis factor α, and mannose-binding lectin (15, 19-21). Bacterial factors are also important determinants of disease. Serogroup C is an independent predictor of death, and certain subgroups are known to be more virulent than others. A recent study of an outbreak in western Canada revealed that the circulating virulent strain was infrequently identified in the at-risk population during the outbreak (22).

Clinical disease manifests as meningitis in 80 to 85% cases, and *N. meningitidis* is currently the most common cause of bacterial meningitis in the United States. Classic findings include headache, fevers, and a petechial rash that begins on the lower extremities with a predilection for areas of pressure. Blood cultures are positive in 50 to 70% of patients, and culture of petechial skin lesions have a sensitivity of nearly 70% (1). Other presentations include bacteremia without sepsis, or meningococcemia, which may occur with or without meningitis. Early signs of meningococcemia include a petechial or purpuric rash, rigors, severe pain in the extremities, and rapid evolution of the illness (23). Meningococcemia, accounting for 10 to 20% of disease, may progress to septicemia, multiorgan system, and adrenal insufficiency (the Waterhouse-Friderichsen syndrome). Our case of meningococcemia presented with purpura fulminans, shock, and death within 8 hours of symptom development. Although there was no clinical evidence of CNS involvement, the diagnosis was confirmed by a positive PCR of the CSF.

Pneumonia occurs in 5 to 15% of cases, but is often unrecognized due to a lack of familiarity with this entity among providers. In addition, isolation of *Neisseria* from respiratory samples may represent pharyngeal colonization versus active infection, since 10% of healthy adults may be carriers (12). Clinical presentation is typically cough, chills, and chest pain; a previous or concurrent upper respiratory infection is common (12). Serogroup Y has a greater

predilection to respiratory involvement (24). Multilobar disease occurs in 40%, and mortality is reportedly rare (25). One of our cases had a multilobar pneumonia due to *N. meningitidis* that was established with autopsy lung tissue showing invasive disease. Concurrently, 6 military recruits at the same training center presented with radiographically confirmed pneumonias and grew *N. meningitidis* from sputum samples; all recruits received a single dose of oral levofloxacin 500 mg for prophylaxis, and no further cases were noted. Other less common presentations of *N. meningitidis* include pericarditis, arthritis, conjunctivitis, pharyngitis, and genital infections (1, 26-28).

A Gram stain of the blood or CSF showing Gram-negative diplococci suggest the diagnosis; bacterial culture PCR is confirmatory. Cultures may be negative after administration of antibiotics and therefore lack sensitivity in clinical cases. Latex agglutination is used most often in meningitis diagnosis, but false-negative results limit large-scale application. PCR may be useful in cases in which cultures are negative, since it does not require live organisms and may provide a more rapid diagnosis than cultures (29). Serogroup-specific (30) PCR primers are also available. PCR or latex agglutination may also be useful postmortem to determine the cause of death, as in two of our cases.

Antibiotic therapy should be immediately instituted with intravenous penicillin G or ceftriaxone. Early or preadmission administration of penicillin has been shown to reduce mortality (2). Strains showing relative resistance to penicillin have been noted, emphasizing the importance of using high-dose penicillin G therapy (4 million units every 4 hours) (31). Chloramphenicol is still utilized in developing countries, although resistant isolates are described (32). Adjunctive steroids are somewhat controversial in *N. meningitidis* meningitis; their use in *H. influenzae* and *Streptococcus pneumoniae* is better defined. Steroids are not indicated for

meningococcemia without meningitis. Use of activated protein C (drotrecogin alfa) is better studied, and levels of protein C in meningococcemia are correlated to outcome. Several studies have suggested activated protein C improves morbidity and mortality, and use of this product should be considered for meningococcemia (33-40). The use of other immunomodulating agents to alter cytokine and endotoxin levels requires further investigation. Mortality rates continue to be high (up to 10%), despite antimicrobial therapy and intensive unit care. Poor prognostic findings include petechiae present for less than 12 hours before presentation, hypotension, absence of meningitis, and low white blood cell count (41). Those with septicemia have mortality rates of 30 to 50% frequently, with death occurring early in the course of the illness (1, 2).

Preventive strategies include the use of the quadrivalent polysaccharide vaccine in high-risk groups, including college freshmen residing in dormitories, military members aboard ship or at training centers, and travelers to areas including sub-Saharan Africa and pilgrimages to Saudi Arabia. The vaccine is 85% or more efficacious against serogroups A, C, Y, and W-135 (42). According to data from 2000 to 2002, the most common serogroups causing clinical disease in the United States are B (40%), Y (29%), and C (24%); most cases are vaccine preventable (43). Unfortunately, the B capsule is poorly immunogenic, and a vaccine is not currently available for this serogroup. Disease may still develop despite vaccination, as seen in our cases. Also, multiple vaccinations may cause tolerance to the polysaccharide antigen. A novel meningococcal group C conjugate vaccine offers the potential advantages of improved T cell-mediated immune response, herd immunity of unvaccinated persons, and an increased duration of protection; it has been shown to decrease both clinical cases and fatalities in the United Kingdom. (44, 45).

Close contacts of a case of meningococcal disease should receive chemoprophylaxis with a fluoroquinolone, such as ciprofloxacin or levofloxacin, rifampin, or ceftriaxone. Disease occurrence due to failed prophylaxis from rifampin-resistant strains is described, but is rare (31). Index cases treated with penicillin should also be treated with a fluoroquinolone or rifampin to assure eradication of the carrier state. This is not needed for those treated with ceftriaxone. Our three cases led to the immediate prophylaxis using levofloxacin 500 mg oral tablet of persons sharing berthing areas; there were no secondary cases.

In summary, meningococcal disease has a variety of presentations, including meningitis, meningococcemia with purpura fulminans, and pneumonia. Cases may occur in all age groups, however, young adults who reside in crowded living conditions are at particular risk. Molecular techniques are a useful adjunct to bacterial cultures when commercially available. Our case series highlights the need for better preventive strategies, including novel vaccines with improved immunogenicity.

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References

1. Memish ZA. Meningococcal disease and travel. Clin Infect Dis 2002; 34:84-90.
2. Cartwright KA. Early management of meningococcal disease. Infect Dis Clin North AM 1999; 13:661-84.
3. Outbreaks of group B meningococcal disease--Florida, 1995 and 1997. MMWR Morb Mortal Wkly Rep 1998; 47:833-7.4.
4. Jackson LA, Alexander ER, DeBolt CA, Swenson PD, Boase J, McDowell MG, Reeves MW, Wenger JD. Evaluation of the use of mass chemoprophylaxis during a school outbreak of enzyme type 5 serogroup B meningococcal disease. Pediatr Infect Dis J 1996; 15:992-8.
5. Popovic T, Schmink S, Rosenstein NA, Ajello GW, Reeves MW, Plikaytis B, Hunter SB, Ribot EM, Boxrud D, Tondella ML, Kim C, Noble C, Mothershed E,. Besser J, Perkins BA. Evaluation of pulsed-field gel electrophoresis in epidemiological investigations of meningococcal disease outbreaks caused by *Neisseria meningitidis* serogroup C. J Clin Microbiol 2001; 39:75-85.
6. Brundage JF, Zollinger WD. Evolution of meningococcal disease epidemiology in the U.S. Army. In: Vedros NA, editor. Evolution of meningococcal disease. Boca Raton, Fla.: CRC Press; 1987. p. 5-23.
7. Fischer M, Hedberg K, Cardosi P, Plikaytis BD, Hoesly FC, Steingart KR, Bell TA, Fleming DW, Wenger JD, Perkins BA. Tobacco smoke as a risk factor for meningococcal disease. Pediatr Infect Dis J 1997; 16:979-83.
8. Young LS, LaForce FM, Head JJ, Feeley JC, Bennett JV. A simultaneous outbreak of meningococcal and influenza infections. N Engl J Med 1972; 287:5-9.
9. Moore PS, Hierholzer J, DeWitt W, Gouan K, Djore D, Lippeveld T, Plikaytis B, Broome CV. Respiratory viruses and mycoplasma as cofactors for epidemic group A meningococcal meningitis. JAMA 1990; 264:1271-5.
10. Figueroa JE, Densen P. Infectious diseases associated with complement deficiencies. Clin Microbiol Rev 1991; 4:359-95.
11. Outbreak of group A streptococcal pneumonia among Marine Corps recruits – California, November 1 – December 20, 2002. MMWR Morb Mortal Wkly Rep 2003 Feb 14;52: 106-9.

12. Rosenstein NE, Perkins BA, Stephens DA, Popovic T, Hughes JM. Meningococcal disease. N Engl J Med 2001; 244:1378-88.
13. Vieusseux M. Mé moire sur la maladie qui a regne' a Geveve au printemps de 1805. J Med Chir Pharmacol 1805; 11:163.
14. Weichselbaum A. Ueber die Aetiologie der akuten Meningitis cerebro-spinalis. Fortschr d Med Berl 1887; v 573;620.
15. Xu W, McDonough MC, Erdman DD. Species-specific identification of human adenoviruses by a multiplex PCR assay. J Clin Microbiol. 2000 Nov; 38(11):4114-20. Erratum in: J Clin Microbiol 2001 Apr; 39(4):1686.
16. Bruce M, Rosenstein NE, Capparella J, Perkins BA, Collins MJ. Meningococcal disease in college students. In: Abstracts of the 39th Annual Meeting of the Infectious Diseases Society of America; 1999 Nov 18-21; Philadelphia, PA. IDSA; 1999.
17. Sumaraju V, Smith LG, Smith SM. Infectious complications in asplenic hosts. Infect Dis Clin North Am 2001; 15:551-65.
18. Merino J, Rodriguez-Valverde V, Lamelas JA, Riestra JL, Casanueva B. Prevalence of deficits of complement components in patients with recurrent meningococcal infections. J Infect Dis 1983; 148:331.
18. Merino J, Rodriquez-Valverde V, Lamelas JA, et al. Prevalence of deficits of complement components in patients with recurrent meningococcal infections. J Infect Dis 1983; 148:331.
19. Nadel S, Newport MJ, Booy R, Levin M. Variation in the tumor necrosis factor-alpha gene promoter region may be associated with death from meningococcal disease. J Infect Dis 1996; 174:878-80.
20. Hibberd ML, Sumiya M, Summerfield JA, Booy R, Levin M. Association of variants of the gene for mannose-binding lectin with susceptibility to meningococcal disease. Meningococcal Research Group. Lancet 1999; 353: 1049-53.
21. Emonts M, Hazelzet JA, de Groot R, Hermans PW. Host genetic determinants of *Neisseria meningitidis* infections. Lancet Infect Dis 2003; 3:565-77.
22. Patrick DM, Champagne S, Goh SH, Arsenault G, Thomas E, Shaw C, Rahim T, Taha F, Bigham M, Dubenko V. Skowronski D, Brunham RC. *Neisseria meningitidis* carriage during an outbreak of serogroup C disease. Clin Infect Dis 2003; 37:1183-8.

23. Yung AP, McDonald MI. Early clinical clues to meningococcaemia. Med J Aust 2003; 178:134-7.
24. Racoosin JA, Whitney CG, Conover C, Diaz PS. Serogroup Y meningococcal disease in Chicago, 1991-1997. JAMA 1998; 280:2094-8.
25. Koppes GM, Ellenbogen C, Gebhart RJ. Group Y meningococcal disease in United States Air Force recruits. Am J Med 1977; 62:661-6.
26. Salzman MB, Rubin LG. Meningococcemia. Infect Dis Clin North Am 1996; 10:709-25.
27. Bonsell S. Isolated knee joint infection with *Neisseria meningitidis*. Orthopedics 2002; 25:537-9.
28. Vikram HR, Buencamino RB, Aronin SI. Primary meningococcal arthritis in a prosthetic knee joint. J Infect 2001; 42:279-81.
29. Pollard AJ, Probe G, Trombley C, Castell A, Whitehead S, Bigham JM, Champagne S, Issac-Renton J, Tan R, Guiver M, Borrow R, Speert DP, Thomas E. Evaluation of a diagnostic polymerase chain reaction assay for *Neisseria meningitidis* in North America and field experience during an outbreak. Arch Pathol Lab Med 2002; 126:1209-15.
30. Baethgen LF, Moraes C, Weidlich L, Rios S, Kmetzsch CI, Silva MS, Rossetti ML, Zaha A. Direct-test PCR for detection of meningococcal DNA and its serogroup characterization: standardization and adaptation for use in a public health laboratory. J Med Microbiol 2003; 52:793-9.
31. Oppenheim BA. Antibiotic resistance in *Neisseria meningitidis*. Clin Infect Dis 1997; 24:S98-101.
32. Galimand M, Gerbaud G, Guibourdenche M, Riou JY, Courvalin P. High-level chloramphenicol resistance in *Neisseria meningitidis*. N Engl J Med 1998;339:868-74. Erratum in N Engl J Med 1999 Mar 11; 340(10):824.
33. Bachli EB, Vavricka SR, Walter RB, Leschinger MI, Maggiorini M. Drotrecogin alfa (activated) for the treatment of meningococcal purpura fulminans. Intensive Care Med 2003;29:337.
34. de Kleijn ED, de Groot R, Hack CE, Mulder PG, Engl W, Moritz B, Joosten KF. Activation of protein C following infusion of protein C concentrate in children with severe meningococcal sepsis and purpura fulminans: a randomized, double-blinded, placebo-controlled, dose-finding study. Crit Care Med 2003;31(6):1839-47.

35. Faust SN, Levin M. Harrison OB, Goldin RD, Lockhart MS, Kondaveeti S, Laszik Z, Esmon CT, Heyderman RS. Dysfunction of endothelial protein C activation in severe meningococcal sepsis. N Engl J Med 2001; 345:408-16.
36. White B, Livingstone W, Murphy C, Hodgson A, Rafferty M, Smith OP. An open-label study of the role of adjuvant hemostatic support with protein C replacement therapy in purpura fulminans-associated meningococcemia. Blood 2000; 96:3719-24.
37. Alberio L, Lammle B, Esmon CT. Protein C replacement in severe meningococcemia: rationale and clinical experience. Clin Infect Dis 2001; 32:1338-46.
38. Rivard GE, David M, Farrell C, Schwarz HP. Treatment of purpura fulminans in meningococcemia with protein C concentrate. J Pediatr 1995;126:646-52.
39. Powars DR, Rogers ZR, Patch MJ, McGehee WG, Francis RB Jr. Purpura fulminans in meningococcemia: association with acquired deficiencies of proteins C and S. N Engl J Med 1987; 317:571-2.
40. Stiehm ER, Damrosch DS. Factors in the prognosis of meningococcal infection Review of 63 cases with emphasis on recognition and management of the severely ill patient. J Pediatr 1966; 68:457-67.
41. Rosenstein NE, Fischer M, Tappero JW. Meningococcal vaccines. Infect Dis Clin North Am 2001; 15:155-69.
42. Harrison L, Pass MA, Mendelsohn AB, Egri M, Rosenstein NE, Bustamante A, Razeq J, Roche JC. Invasive meningococcal disease in adolescents and young adults. JAMA 2001; 286:694-9.
43. Ruggeberg J, Heath PT. Safety and efficacy of meningococcal group C conjugate vaccines. Expert Opinion on Drug Safety 2003; 2:7-19.
44. Balmer P, Borrow R, Miller E. Impact of meningococcal C conjugate vaccine in the UK. J Med Microbiol 2002; 51:717-22.

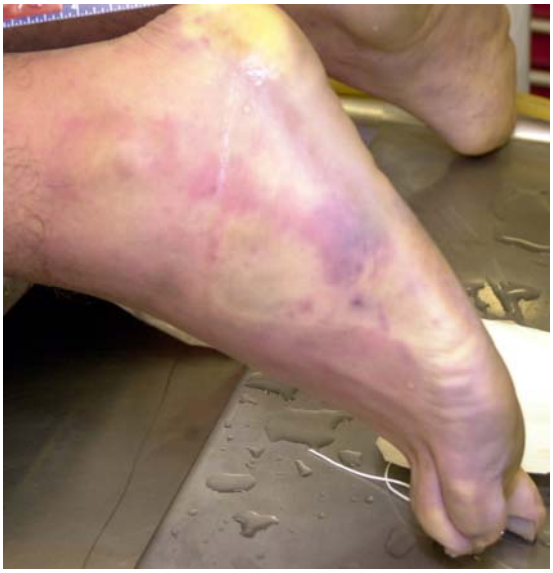

Figure 1: Rash of purpura fulminans on lower extremity.

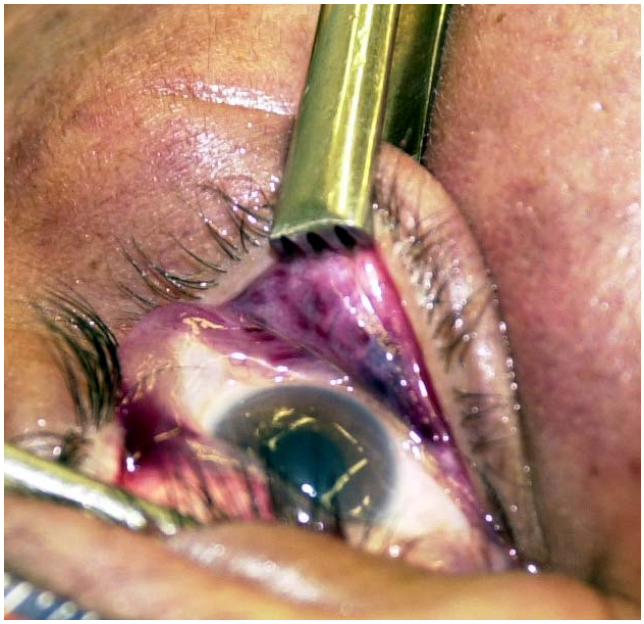

Figure 2: Palpebral conjunctival petechiae.

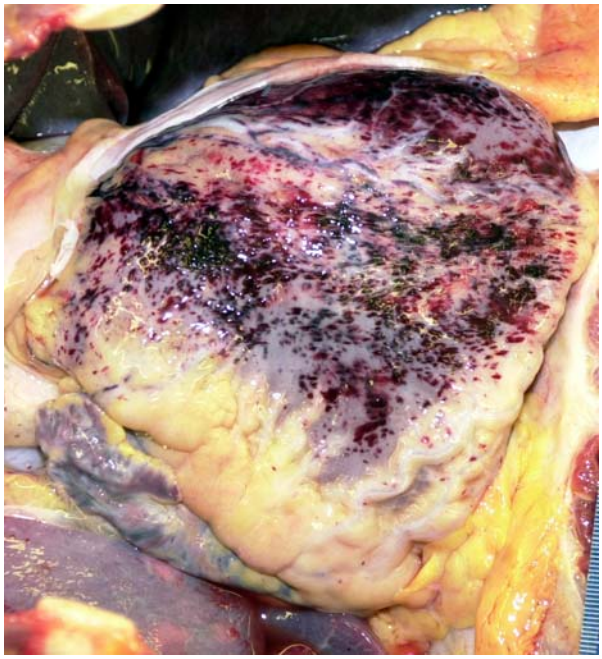

Figure 3: Petechiae of the epicardium on postmortem examination.

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